24. The method for reducing atherosclerotic plaque formation at sites of endothelial damage in humans of claim 11, further comprising decreasing standard clot formation through the oral administration of selenium as said medicament.

25. The method for reducing atherosclerotic plaque formation at sites of endothelial damage in humans of claim 11, further comprising decreasing immune-induced lesions through the oral administration of at least one trace element selected from the group consisting copper and selenium as said medicament.

Cl cont.

26. The method for reducing atherosclerotic plaque formation at sites of endothelial damage in humans of claim 11, further comprising decreasing peroxidation through the oral administration of selenium as said medicament.

Kindly delete claims 1-10.

REMARKS

Additional claims have been added to further distinguish the application over the prior art, so as to place the application, as a whole, into a prima facie condition for allowance. Great care has been taken to avoid the introduction of new subject matter into the application as a result of the foregoing modifications.

The claims have been rewritten to claim a method rather than a medicament to emphasize the synergistic effect of blocking prostaglandin function in platelets through the oral administration of aspirin in conjunction with a reduction in the migration of cholesterol into the endothelium through the oral administration of a medicament such as a medicament. Support for these claims can be found in the specification which is a detailed explanation of the synergistic activity of aspirin in conjunction with various medicaments.

The Examiner has objected to the specification under 35 U.S.C. §112 since the proportions of active agents present in the synergistic compositions are not clearly set forth in the specification. Applicant's specification does not list specific dose ranges for aspirin and for the vitamins and minerals noted in the specification, since appropriate dose ranges for aspirin, vitamins, and minerals are well known to those of ordinary skill in the art. The dosages of aspirin and medicaments vary greatly with the particular individual being treated. Since the claimed invention relates to a method for blocking prostaglandin function and reducing the migration of cholesterol with aspirin and medicaments, it is well within the skill of the art to provide a proper dosage of aspirin and medicament concomitant with the age, weight, and medical history of the individual being treated.

The Examiner has stated that there is no clear showing of the synergistic activity of the claimed composition and pharmaceutical effect. Applicant respectfully submits that "the absence of synergism is irrelevant to the issue of obviousness. Synergism is probative only of non-obviousness." Ryko Manufacturing Co. v. Nu-Star, Inc., 950 F.2d 714, 21 U.S.P.Q.2d 714, 21 U.S.P.Q.2d 1053, 1056 (Fed. Cir. 1991). "Though synergism is relevant when present, its 'absence' has no place in evaluating the evidence on obviousness.'" Custom Accessories, Inc. v. Jeffrey-Allan Industries, Inc., 807 F.2d 955, 1 U.S.P.Q.2d 1196 (Fed. Cir. 1986).

Notwithstanding the foregoing, Applicant submits a graphic representation of the previously submitted University of Southern California study on the effects of aspirin and the incidence of cardiovascular diseases. From the graphical

representation of the data, one can clearly see with the naked eye that the anticipated effects of the combination of aspirin and vitamin are far less than the actual effects noted in both the table and the graphic representation. The actual effects of the combination of aspirin and vitamin are far in excess of a mere additive effect anticipated by the combination of aspirin with the vitamin on all deaths, total cardiovascular deaths, myocardial infarction, ischemic heart disease, and other heart disease. Indeed, the anticipated effect for all deaths is deliterious, while the actual effect is quite beneficial. This evidence is buttressed by the affidavit of Dr. Larry H. Hollier submitted herewith. In his Declaration, Dr. Hollier states that the graphic representation of the data collected in the University of Southern California study shows that the anticipated benefits of combining the weekly combination of aspirin with the administration of vitamins would be detrimental to the health of individuals so treated. Dr. Hollier states that in stark contrast to the anticipated effect, the actual effect of the weekly administration of aspirin in combination with vitamins is unanticipatedly beneficial to individuals so treated.

It is respectfully submitted that this remarkable synergism, combined with the absence of prior art suggesting or otherwise making the method of the present invention obvious to one of ordinary skill in the art, overcomes the present rejection for obviousness. In re Corkill, 771 F.2d 1496, 226 U.S.P.Q. 1005 (Fed. Cir. 1985).

On January 7, 1994, the Examiner granted Applicant an interview for which Applicant thanks the Examiner. During the interview, the Examiner discussed the issue of inventorship and questioned whether the persons performing the U.S.C. test would qualify as inventors of the present invention. Applicant respectfully

submits that not only was the objective of the U.S.C. test merely "to evaluate the associations between the use of aspirin and the incidences of cardiovascular diseases, cancers, and other chronic diseases" but the data submitted herewith correlating aspirin and vitamin use had not been prepared or sought until requested by Applicant for this application. The U.S.C. test addressed only aspirin use relative to various diseases. Fortunately, when the test was conducted, participants were routinely asked a broad array of questions, one of which was the regularity of vitamin use. Applicant requested from the U.S.C. officials the raw data concerning aspirin and vitamin use with respect to various heart diseases. As can be seen from both the attached raw data and graphic representation, the data extracted from the U.S.C. test by Applicant supports the present application. Furthermore, since the U.S.C. test did not involve the examination of the effects of vitamin use, and since information regarding vitamins had not even been tabulated until the request from Applicant, the persons involved with the U.S.C. test could not be inventors of the present invention.

Since the U.S.C. test was not conducted to evaluate vitamin use in conjunction with aspirin, the types of vitamins used by participants was not noted. Applicant, however, submits herewith evidence that the most typical vitamins used by individuals include the medicaments noted in the present application. Applicant submits an excerpt from the Share Reporter which notes that over 50 percent of the market share for vitamins consists of Centrum, One-A-Day, and store brands. Applicant also submits labels from Centrum, One-A-Day, and a store brand, all of which contain the medicaments listed in the present application. In further support

of Applicant's position, the Examiner is respectfully referred to the Declaration of Dr. Hollier which notes that multivitamins are the most typical type of over-the-counter vitamin supplement taken by the general public and that most multivitamin tablets contain the vitamins and minerals claimed in the present application.

Accordingly, the purpose of the claimed invention is not taught nor suggested by the cited references, nor is there any suggestion or teaching which would lead one skilled in the relevant art to administer aspirin in conjunction with the claimed medicaments to achieve the synergism previously noted. Applicant respectfully submits that the anticipated combination of aspirin and medicaments would actually lead one skilled in the relevant art to assume such a combination would lead to an increase in deaths. As the submitted evidence shows, however, and as supported by Dr. Hollier, the actual combination shows unexpectedly synergistic results leading to a decrease in deaths and cardiovascular diseases.

Based on the foregoing, Applicant respectfully submits that its claims 11-26 are in condition for allowance at this time, patentably distinguishing over the cited prior art. Accordingly, reconsideration of the application and passage to allowance are respectfully solicited.

The Examiner is respectfully urged to call the undersigned attorney at (515) 288-2500 to discuss the claims in an effort to reach a mutual agreement with respect to claim limitations in the present application which will be effective to define the patentable subject matter if the present claims are not deemed to be adequate for this purpose.

Respectfully submitted,

Date: March 10, 1994

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I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231, on

March 10, 1994

By Kent A. Herink

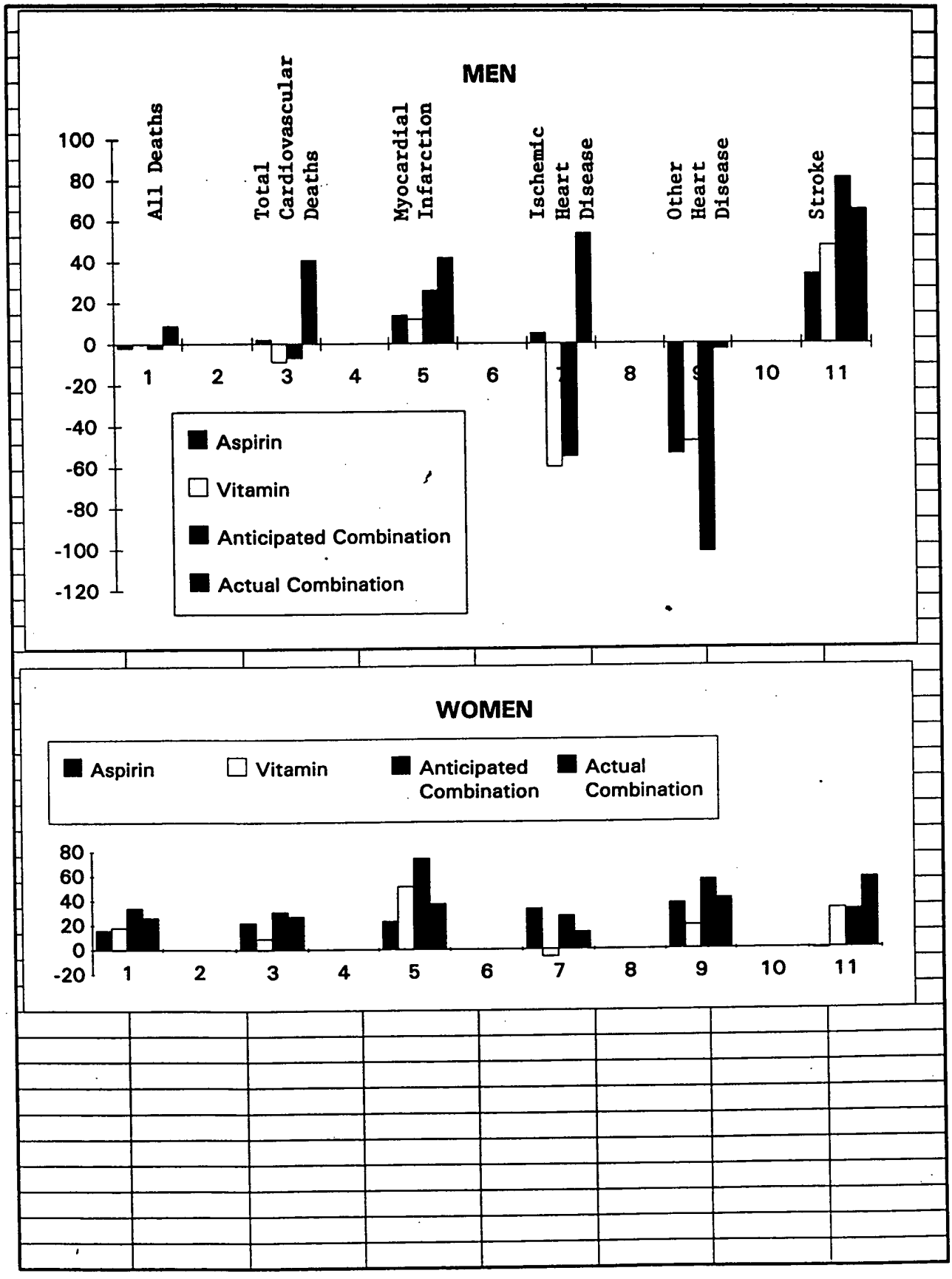
MEN
All Deaths
Total Cardiovascular Deaths
Myocardial Infarction
Ischemic Heart Disease
Other Heart Disease
Stroke
100
80
60
40
20
0
-20
-40
-60
-80
-100
-120
1
2
3
4
5
6
8
10
11
Aspirin
Vitamin
Anticipated Combination
Actual Combination
WOMEN
Aspirin
Vitamin
Anticipated Combination
Actual Combination
80
60
40
20
0
-20
1
2
3
4
5
6
7
8
9
10
11

TABLE 3

Aspirin and Vitamin Use	All Deaths		Total Cardiovascular Deaths		Myocardial Infarction		Ischemic Heart Disease		Other Heart Disease		Stroke	
	No.	RR	No.	RR	No.	RR	No.	RR	No.	RR	No.	RR
Men:												
Aspirin- Vitamin-	320	1.00	161	1.00	54	1.00	45	1.00	29	1.00	29	1.00
Aspirin- Vitamin+	450	1.02	203	0.92	64	0.86	58	0.95	58	1.46	26	0.66
Aspirin+ Vitamin-	45	1.00	24	1.09	7	0.88	8	1.40	6	1.52	2	0.52
Aspirin+ Vitamin+	91	0.91	29	0.59	10	0.58	6	0.46	9	1.03	3	0.34
Aspirin++ Vitamin-	65	1.35	27	1.09	7	0.91	10	1.37	7	1.57	7	1.53
Aspirin++ Vitamin+	112	1.01	51	0.90	11	0.61	13	0.78	13	1.26	12	1.16
Vitamin+		0.96		0.85		0.80		0.78		1.07		0.69
Women:												
Aspirin- Vitamin-	326	1.00	166	1.00	46	1.00	50	1.00	44	1.00	33	1.00
Aspirin- Vitamin+	561	0.84	263	0.78	72	0.77	69	0.67	57	0.63	67	1.01
Aspirin+ Vitamin-	47	0.82	26	0.91	4	0.49	9	1.06	6	0.81	4	0.68
Aspirin+ Vitamin+	119	0.74	58	0.73	14	0.63	20	0.86	12	0.59	7	0.43
Aspirin++ Vitamin-	77	1.36	45	1.48	10	1.25	14	1.50	12	1.41	9	1.58
Aspirin++ Vitamin+	163	1.08	86	1.10	24	1.13	23	0.97	24	1.14	14	0.92
Vitamin+		0.85		0.78		0.83		0.70		0.68		0.87

Aspirin use: - = none; + = weekly or less often; ++ = daily
Vitamin use: - = no; + = yes

SHARE REPORTER

AN ANNUAL COMPILATION
OF REPORTED MARKET SHARE
DATA ON COMPANIES,
PRODUCTS, AND SERVICES

1991

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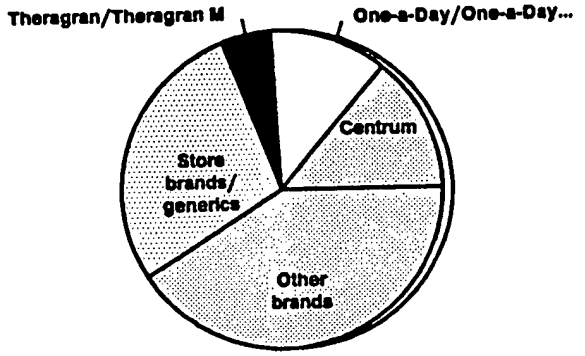
Gale Research Inc. • DETROIT • LONDON

★722★
Drugs (SIC 2834)

Vitamin Market - Adult



Leading brands and manufacturers; shares in percent.

Centrum (Lederle)	14.0%
One-a-Day/One-a-Day with Iron (Miles)	12.0
Theragran/Theragran M (Squibb)	5.0
Store brands/generics	28.0
Other brands	41.0

Source: *Drug Topics*, January 8, 1990, p. 46.

★723★
Drugs (SIC 2834)

Vitamin Market - Baby

Leading brands and manufacturers; shares in percent.

Poly-Vi-Sol (Mead Johnson)	57.0%
Flintstones (Miles)	21.0
Tri-Vi-Sol (Mead Johnson)	7.0
Other brands	15.0

Source: *Drug Topics*, January 8, 1990, p. 48.

★724★
Drugs (SIC 2834)

Vitamin Market - Child

Leading brands and manufacturers; shares in percent.

Flintstones (Miles)	34.0%
Store brands/generics	23.0
Poly-Vi-Sol (Mead Johnson)	6.0
Sunkist (Ciba)	5.0
Other brands	32.0

Source: *Drug Topics*, January 8, 1990, p. 48.

★725★
Drugs (SIC 2834)

World Ulcer Drugs - Brands

Shares of the peptic ulcer remedy market in 1989, shown in percent by brand.

Zantac (ranitidine)	44.0%
Tagamet (cimetidine)	22.0
Gaster/Pepcid (famotidine)	8.0
Axid (nizatidine)	2.0
Altat (roxatidine)	<1

Source: Investext, Thomson Financial Networks, January 1, 1990 from Smith New Court Securities PLC.

★726★
Drugs (SIC 2834)

World Ulcer Drugs - Producers

Shares of the peptic ulcer remedy market in 1989, shown in percent.

Glaxco	44.0%
Smithkline Beecham	22.0
Yamanouchi/Merck	8.0
Eli Lilly	2.0
Teikoku Hormone/Hoechst	<1

Source: Investext, Thomson Financial Networks, January 1, 1990 from Smith New Court Securities PLC.

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13 vitamins
18 minerals

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30 tablets

USE ONLY IF PRINTED INNER FOIL SEAL IS NOT BROKEN OR MISSING.
Directions: Adults, Young Adults, one tablet daily or as directed by a physician.

EACH TABLET CONTAINS:		%U.S. RDA*
Vitamin A (as Acetate)	2000 I.U.	40
Beta Carotene (3.6 mg.)	6000 I.U.	120***
Vitamin E (as dl-Alpha Tocopheryl Acetate)	30 I.U.	100
Vitamin C (as Niacinamide Ascorbate)	90 mg.	150
Folic Acid	400 mcg.	100
Vitamin B-1 (as Thiamine Mononitrate)	5 mg.	333
Vitamin B-2 (as Riboflavin)	5 mg.	294
Niacin (as Niacinamide Ascorbate)	30 mg.	150
Vitamin B-6 (as Pyridoxine Hydrochloride)	5 mg.	250
Vitamin B-12 (as Cyanocobalamin)	12 mcg.	200
Vitamin D	400 I.U.	100
Biotin	40 mcg.	13
Pantothenic Acid (as Calcium Pantothenate)	10 mg.	100
Vitamin K-1 (as Phytonadione)	25 mcg.	**
Calcium (as Dicalcium Phosphate)	162 mg.	16
Phosphorus (as Dicalcium Phosphate)	125 mg.	13
Iodine (as Potassium Iodide)	150 mcg.	100
Iron (as Ferrous Fumarate)	25 mg.	139
Magnesium (as Magnesium Oxide)	100 mg.	25
Copper (as Cupric Oxide)	3 mg.	150
Manganese (as Manganese Sulfate)	7.5 mg.	**
Potassium (as Potassium Chloride)	7.7 mg.	**
Chloride (as Potassium Chloride)	7 mg.	**
Zinc (as Zinc Oxide)	15 mg.	100
Chromium (as Chromium Chloride)	50 mcg.	**
Selenium (as Sodium Selenate)	50 mcg.	**
Molybdenum (as Sodium Molybdate)	50 mcg.	**
Tin (as Stannous Chloride)	10 mcg.	**
Vanadium (as Sodium Metavanadate)	10 mcg.	**
Nickel (as Nickelous Sulfate)	5 mcg.	**
Silicon (as Metasilicates and Oxides)	2 mg.	**
Boron (as Borates)	150 mcg.	**

* %U.S. Recommended Daily Allowance for adults and children 4 or more years of age.
** Recognized as essential in human nutrition but no U.S. RDA established.
*** U.S. RDA not established. Partial conversion to Vitamin A occurs in the body, up to a maximum 6000 I.U.

Plus excipients and artificial colors (FD&C Blue No. 2, FD&C Red No. 40, Titanium Dioxide).
KEEP OUT OF REACH OF CHILDREN.
KEEP TIGHTLY CLOSED. Store at controlled room temperature between 15° and 30°C (59° and 86°F). Use by expiration date printed on package.

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NDC 0005-4239-19

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HIGH POTENCY MULTIVITAMIN-MULTIMINERAL FORMULA

From A to Zinc INCLUDING THE COMPLETE ANTIOXIDANT GROUP

EACH TABLET CONTAINS:		For Adults—Percentage of U.S. Recommended Daily Allowance (U.S. RDA)
Vitamin A (as Acetate and Beta Carotene)	5000 IU	(100%)
Vitamin D	400 IU	(100%)
Vitamin E	30 IU	(100%)
Vitamin K1	25 mcg*	
Vitamin C	60 mg	(100%)
Folic Acid	400 mcg	(100%)
Vitamin B1	1.5 mg	(100%)
Vitamin B2	1.7 mg	(100%)
Niacinamide	20 mg	(100%)
Vitamin B6	2 mg	(100%)
Vitamin B12	6 mcg	(100%)
Pantothenic Acid	10 mg	(100%)
Biotin	30 mcg	(10%)
Calcium	162 mg	(16%)
Phosphorus	109 mg	(11%)
Iodine	150 mcg	(100%)
Iron	18 mg	(100%)
Magnesium	100 mg	(25%)
Copper	2 mg	(100%)
Zinc	15 mg	(100%)
Manganese	2.5 mg*	
Potassium	40 mg*	
Chloride	36.3 mg*	
Chromium	25 mcg*	
Molybdenum	25 mcg*	
Selenium	20 mcg*	
Nickel	5 mcg*	
Tin	10 mcg*	
Silicon	2mg*	
Vanadium	10 mcg*	
Boron	150 mcg*	

RECOMMENDED INTAKE:
Adults, 1 tablet daily.
Keep this and all medications out of the reach of children.
Store at Room Temperature.

Inactive Ingredients: FD&C Yellow No 6, Hydroxypropyl Methylcellulose, Lactose, Magnesium Stearate, Microcrystalline Cellulose, Polysorbate 80, Polyvinylpyrrolidone, Stearic Acid Titanium Dioxide and Triethyl Citrate.

*No U.S. RDA established.

D30

Control No.,
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N 3 0005-4239-19 8

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MULTIVITAMIN / MULTIMINERAL SUPPLEMENT

DIRECTIONS FOR USE:
Adults take one tablet daily.

VITAMINS	QUANTITY	% U.S. RDA	MINERALS	QUANTITY	% U.S RDA
Vitamin A (as Acetate and Beta Carotene)	5000 I.U.	100	Iron (elemental)	18 mg	100
			Calcium (elemental)	130 mg	13
Vitamin C	60 mg	100	Phosphorus	100 mg	10
Thiamine (B-1)	1.5 mg	100	Iodine	150 mcg	100
Riboflavin (B-2)	1.7 mg	100	Magnesium	100 mg	25
Niacin	20 mg	100	Copper	2 mg	100
Vitamin D	400 I.U.	100	Zinc	15 mg	100
Vitamin E	30 I.U.	100	Chromium	10 mcg	*
Vitamin B-6	2 mg	100	Selenium	10 mcg	*
Folic Acid	0.4 mg	100	Molybdenum	10 mcg	*
Vitamin B-12	6 mcg	100	Manganese	2.5 mg	*
Biotin	30 mcg	10	Potassium	37.5 mg	*
Pantothenic Acid	10 mg	100	Chloride	34 mg	*

*No. U.S. RDA established

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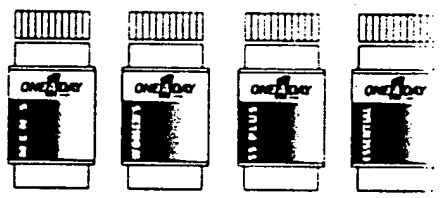

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